

Complete heart block in a boy with hyperostosis–hyperphosphataemia syndrome: a case report

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Received 12 July 2018; accepted 18 January 2019; online publish-ahead-of-print 5 February 2019

Background

Hyperostosis–hyperphosphataemia syndrome (HHS) is a rare metabolic disorder characterized by recurrent painful swelling of long bones and periosteal new bone formation.

Case summary

A 6-year-old boy was referred to our centre due to bradycardia. He was diagnosed with HHS 3 years' prior, after investigation for the cause of joint pain and genu valgum. During medical follow-up in 2013–16, the paediatric cardiologist discovered thickened and calcified mitral and aortic valves and progression of cardiac conduction disturbance from 1st degree to 3rd degree atrioventricular block (AVB). The patient died in 2017 due to multiorgan failure caused by hyperphosphataemia and ectopic calcification.

Discussion

Our case is unique in that ectopic calcification occurred in the aortic, mitral valve and cardiac conduction system, and AVB progressed from 1st degree to 3rd degree over time despite treatment with high-dose phosphate binders.

Keywords

Hyperostosis–hyperphosphataemia syndrome • Electrocardiography • Atrioventricular block • Case report • Complete heart block

Learning points

- This case report highlights the first reported atrioventricular block due to phosphate deposition among patients affected with hyperostosis–hyperphosphataemia syndrome.
- Although some patients with this syndrome may survive to adulthood, but severe forms may not survive in childhood due to the severity of cardiac involvement.

Introduction

Hyperphosphataemic familial tumoural calcinosis/hyperostosis–hyperphosphataemia syndrome (HHS) is a rare autosomal recessive disorder caused by mutations in the genes encoding one of the following: fibroblast growth factor 23 (FGF23), UDP-GalNAc: polypeptide N-acetylgalactosaminyltransferase-T3 (GalNAc-T3), or Klotho.^{1,2} The mutations causing HHS result in relative deficiency of, or resistance to, iFGF23, which leads to hyperphosphataemia, due to

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Handling Editor: Borislav Dinov

Peer-reviewers: Rami Riziq, Yousef Abumuaileq, and Gianluigi Savarese

Compliance Editor: Peregrine Green

Supplementary Material Editor: Mohammed Akhtar

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increased renal tubular reabsorption of phosphate, and elevated or inappropriately normal 1, 25 vitamin D production, which promotes gastrointestinal absorption of phosphorus and calcium. The net effect is an increase in the calcium phosphate product. Affected individuals develop ectopic calcifications and/or diaphyseal hyperostosis, which may manifest clinically as diaphyseal pain of the long bones and periosteal new bone formation.^{1,2} Cardiac involvement is rare and occurs due to uncontrolled hyperphosphataemia and ectopic calcification of heart valves and coronary arteries, but usually is not the leading cause of death in affected patients.² Herein, we present a novel cardiac complication as progressive atrioventricular block (AVB) in this syndrome due to phosphate deposition on the cardiac valves and conduction system.

Timeline

2013	Left knee painful swelling-evaluation and diagnosed with hyperostosis-hyperphosphataemia syndrome (HHS). ECG screening showed 1st degree atrioventricular block (AVB).
2014	Facial nerve palsy. Progression of cardiac conduction disorder to Mobitz I AVB. Echocardiography showed thick and calcified aortic and mitral valves. Genetic study confirmed HHS. The patient was commenced on phosphate binders to decrease ectopic calcification complications.
2015	Due to refractory hyperphosphataemia and end organ damage, the dose of phosphate binders was increased.
2016	Increase in mitral valve calcification leading to mild mitral stenosis, Progression of AVB to 3rd degree. Due to multiorgan dysfunction, close surveillance was decided, and pacemaker was not implanted.
2017	Acetazolamide was added to the treatment regimen due to refractory hyperphosphataemia. Death occurred as the result of multiple organ failure.

Case presentation

A 6-year-old boy was referred to our centre (Imam Khomeini Hospital) by our paediatrician colleagues due to bradycardia found during physical examination which was confirmed by ECG as 3rd degree AVB. Due to dyspnoea and 3rd degree AVB, need for permanent pacemaker implantation was proposed for the patient.

The boy was the only offspring of the unrelated parents. He was diagnosed at the age of 3 years during workup for painful swelling of his left knee and genu valgum when hyperphosphataemia was detected (9.6 mg/dL; normal range: 2.7–4.5 mg/dL). This was the sole symptom at that time. Left knee X-ray showed hyperostosis and periarticular calcification. At the age of 4 years, he developed dental abnormalities, facial nerve palsy, and decreased visual acuity. The physician in charge suspected osteopetrosis as the underlying disease, and therefore, scheduled him for bone marrow transplantation as a

curative treatment (although finally delisted after the diagnosis of HHS and taking into account that bone marrow transplantation has no role in the treatment of HHS). Despite treatment with high-dose Sevelamer (non-calcium phosphate binder) in 2015, the serum phosphate level remained high (8.6 mg/dL). Other serum biomarkers were calcium = 10 mg/dL (normal range: 8.5–10.4 mg/dL), creatinine = 0.5 mg/dL (normal range for children up to 12 years old: 0.0–0.7), PTH = 30 pg/mL (normal range: 9–64 pg/mL), and 25 (OH) vitamin D = 50 pg/mL (normal range: 15–60 pg/mL). Genetic assessment did not show any mutations in the T-Cell Immune Regulator 1 (*TClRG1*) or Chloride Voltage-Gated Channel 7 (*CLCN7*), the usual mutations in the setting of osteopetrosis. Further genetic studies showed a mutation in Fibroblast Growth Factor 23 (*FGF23*) (homozygous mutation in exon 3).¹ This finding was consistent with the diagnosis of HHS.

Cardiology evaluations began in 2013: bradycardia found during physical examination which was confirmed by ECG. Electrocardiography showed 1st degree AVB (Figure 1A). In 2014, electrocardiography was suggestive of Mobitz I (Wenckebach) block (Figure 1B). At that time the patient had dyspnoea on exertion. Echocardiography revealed normal left ventricular systolic and diastolic function (left ventricular ejection fraction was 55% and normal tissue Doppler indices of lateral mitral annulus), aortic valve calcification (without significant stenosis), and mitral stenosis (mean mitral valve gradient was 3 mmHg and mitral valve area was 1.7 cm²). In 2016, the patient developed complete AVB (Figure 1C). Physical examination revealed blood pressure 100/60 mmHg, variable first heart sound and jugular venous pulsation (cannon A wave). Twenty-four hour ECG Holter monitoring showed CHB with a junctional escape rhythm of 70–80 b.p.m. (Figure 2). Echocardiography showed normal left ventricular systolic and diastolic function (left ventricular ejection fraction was 55% and normal tissue Doppler indices of lateral mitral annulus), thick and calcified mitral valve leaflets, calcified chordae, and significant mitral annular calcification leading to mitral stenosis (mitral valve area: 1.4 cm², mean mitral valve gradient = 4 mmHg) (Figure 3) (Supplementary material online, Videos S1 and S2). Aortic and pulmonic valves were also affected (peak aortic transvalvular gradient was 15 mmHg, and also aortic valve calcification was present).

The heart team discussed the risk and benefit of pacemaker in this boy with multiple organ involvement and the risk of general anaesthesia. The family decided to postpone pacemaker implantation taking into account that the patient was asymptomatic (no syncope or pre-syncope), presence of junctional escape rhythm (75–80/min), minimum heart rate of 56/min and absence of pause in Holter monitoring. Treatment with high-dose phosphate binders and then acetazolamide (as the last resort) was required to keep the serum phosphate level at 9–10 mg/dL. In December 2017, he developed progressive multiple organ failure (kidney, liver, heart, and lung) due to phosphate deposition and died in the hospital. Prior to death, CHB with regular narrow QRS escape rhythm was present.

Discussion

Hyperostosis-hyperphosphataemia syndrome is a rare autosomal recessive disorder caused by mutations in the genes encoding *FGF23*

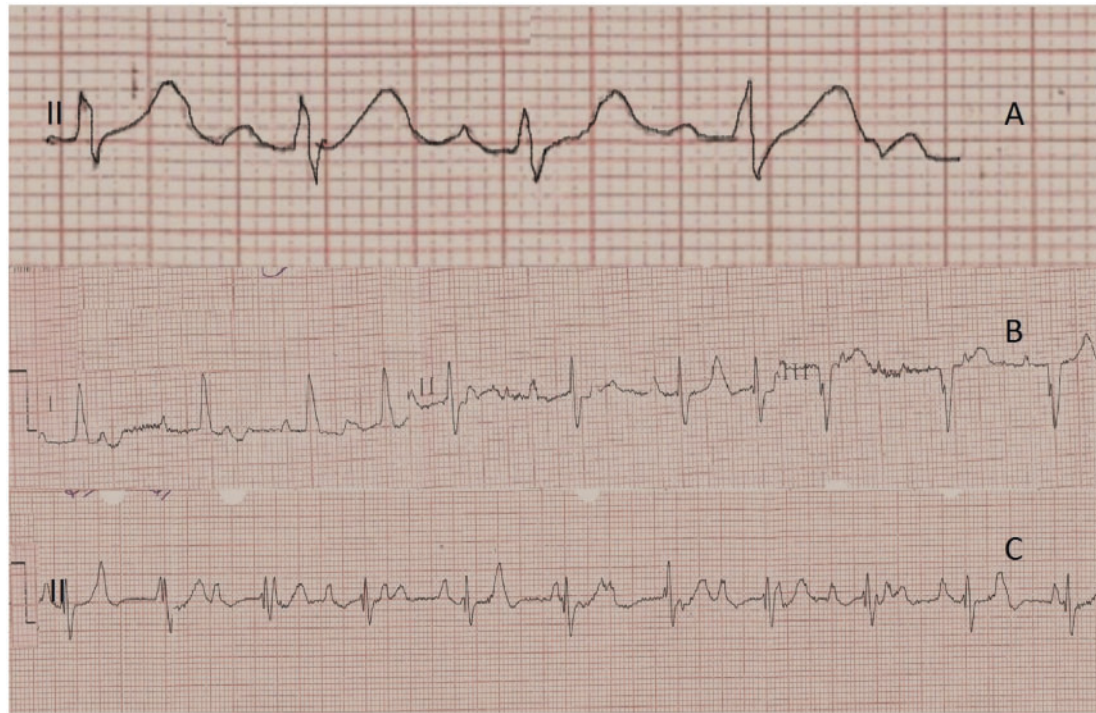


Figure 1 (A) ECG strip of lead II which shows prolonged PR interval = 160 ms (normal range: 80–150 ms for this age group; he was 3 years old in 2013; due to low quality it is bolded). (B) ECG shows group beating and Wenckebach periodicity (he was 4 years old in 2014). (C) Complete heart block is evident in ECG (he was 7 years old in 2017).

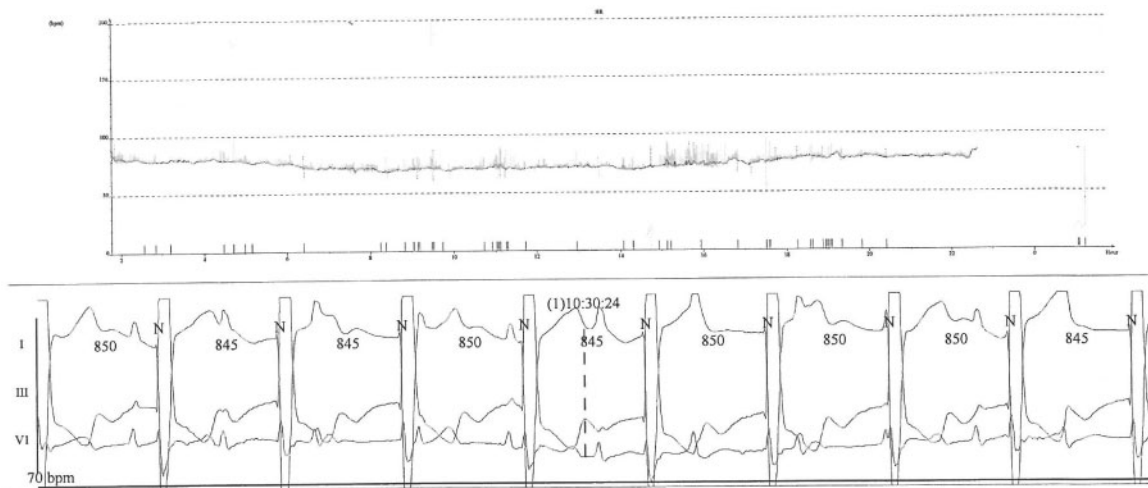


Figure 2 A 24-h ECG Holter monitoring which shows complete atrioventricular block with relatively fixed heart rate (70–80/min).

(as in our patient) and N-acetyl galactosaminyl transferase 3 (*GALNT3*) (the most common mutation).² The mutation in the *FGF23* results in relative deficiency of or resistance to *FGF23*, leading to decreased renal phosphate excretion and inappropriately (high) normal 1, 25 vitamin D, resulting in facilitation of the absorption of

phosphate from the intestine. The net effect would be an increase in the phosphate calcium product (in our patient: $9.6 \times 10 = 96 \text{ mg}^2/\text{dL}^2$ before treatment and $8.6 \times 10 = 86 \text{ mg}^2/\text{dL}^2$ after treatment with Sevelamer). According to the National Kidney Foundation of Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines, the

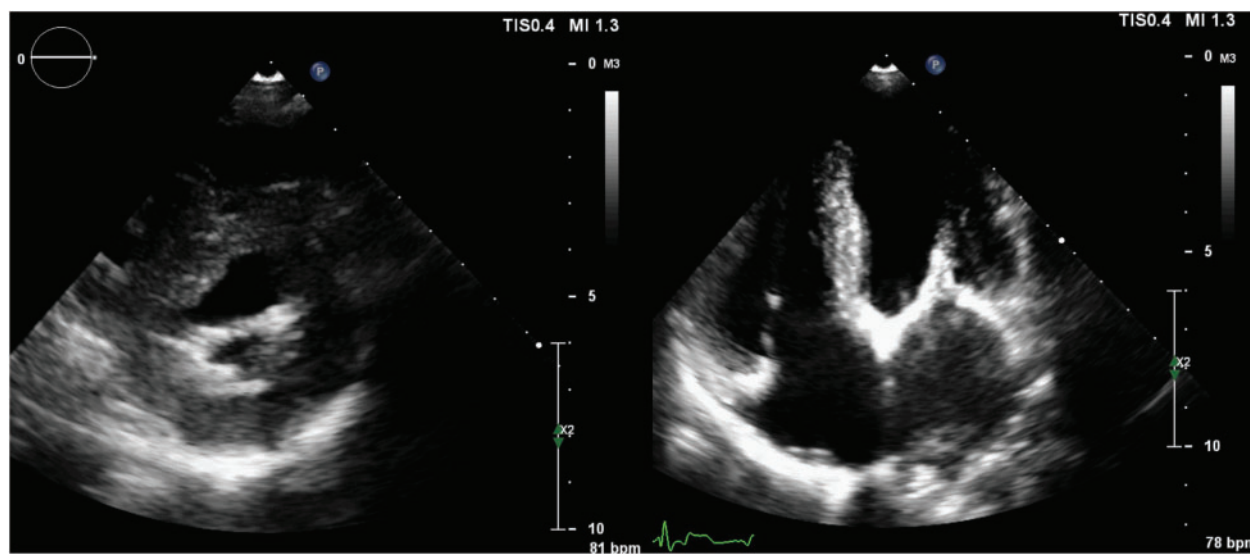


Figure 3 Echocardiography shows thick and calcified mitral valve.

level of this product should be below $65 \text{ mg}^2/\text{dL}^2$ in children aged <12 years.³ Overall, it leads to ectopic calcification and/or diaphyseal hyperostosis.

Cardiovascular complications in HHS reported so far include coronary artery calcification detected on cardiac computed tomography angiography, and papillary muscle calcification.^{2,4} Our case is unique in that ectopic calcification occurred in the aortic and mitral valve as well as the cardiac conduction system, and AVB progressed from 1st degree to 3rd degree overtime despite treatment with high-dose phosphate binders. Our assumption was that AVB might be resolved after treatment of hyperphosphataemia, as previously reported in other reversible diseases.⁵ It is possible that a diagnosis was made too late in this patient, and the treatment started after irreversible destruction of the cardiac conduction system occurred. In the last year of his life, acetazolamide was added to Sevelamer to increase phosphaturia and decrease the serum phosphate level^{5,6} with frequent monitoring of serum bicarbonate level. With all of these measures, we could hardly ever reduce the phosphate level below 9 mg/dL .

Conclusion

Our case is unique in that ectopic calcification occurred in the aortic, mitral valve and cardiac conduction system, and AVB progressed from 1st degree to 3rd degree overtime despite treatment with high-dose phosphate binders.

Ethical standards

Informed consent was obtained from child's parent, and the study was approved by Tehran University of Medical Sciences.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient's parent in line with COPE guidance.

Conflict of interest: none declared.

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